REMARKS

Claims 1-11, 16, 18-21, 24, 25, 30-32 and 36-39 are pending in the instant application. Claims 3, 8, 9, 16, 18-21, 24, 25, 30-32 and 37-38 have been withdrawn from consideration by the Examiner. Claims 1, 2, 4-7, 10-11, 36 and 39 have been rejected. Reconsideration is respectfully requested in light of the Declaration of Dr. Robert Wolfert provided herewith and the following remarks.

I. Amendments to Specification

The specification has been amended to correct inadvertent typographical errors in table numbering. No new matter is added by the amendments. Entry of these amendments is respectfully requested.

II. Election/Restrictions

The Examiner has withdrawn claims 3, 8-9, 16, 18-21, 24-25, 30-32 and 37-38 as being drawn to a nonelected invention/species. It is respectfully pointed out that the claims should only be restricted to the elected species if no generic claim is held allowable. See MPEP § 809.01 and 37 CF.R. § 1.146. Arguments set forth herein make clear that the generic claim is allowable over the cited art. Accordingly, rejoinder of additional species is respectfully requested upon such allowance.

III. Rejection of Claims under 35 U.S.C. 102(b) and 35 U.S.C. 103(a)

Claims 1, 2, 4-7, 11, 36 and 39 have been rejected under 35 U.S.C. 102(b) as being anticipated by Packard et al. (NEJM 2000 343:1148-1155).

Claims 1-2, 4-7, 10-11, 36 and 39 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Packard et al. (NEJM 2000 343:1148-1155) and further in view of Rao et al. (US 2003/0120134).

Applicants respectfully traverse these rejections.

Arguments presented by Applicants in the response filed July 15, 2008 that Packard et al. in no way teaches use of the combined risks of Lp-PLA2 and CRP to assess the risk of CVD in a patient as claimed were deemed unpersuasive. In response to these arguments, the Examiner suggests that no specific definition is provided for the word "combine" in the instant specification and therefore this term is given its broadest reasonable interpretation. The Examiner suggests that Packard et al. confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 'discussion' section 1st paragraph). Further, the Examiner suggests that Packard et al. teach that a model is used to calculate risks and the model uses variables

including Lp-PLA2 and CRP (Table 5). The Examiner therefore suggests that the model of Packard et al. uses a combination of risks. The Examiner also suggests that no special definition is provided for the word 'assess' and therefore this term is given its broadest reasonable interpretation. The Examiner suggests that Table 5 is entitled 'Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event'. The Examiner therefore suggests that the model uses a combination of variables including Lp-PLA2 and CRP to assess risk. The Examiner suggests that to perform the analysis or intended use, Packard et al. carried out active steps that meet the instant claim limitations. The Examiner suggests that since the active steps of the claims are taught by Packard the claim limitations are necessarily met.

Applicants respectfully traverse this rejection.

The Federal Circuit's *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the "broadest reasonable interpretation" standard: The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable

construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). MPEP 2111 and the case law are clear; the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Also see *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 67 USPQ2d 1132, 1136 (Fed. Cir. 2003) holding that in the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art."

In an earnest effort to advance the prosecution of this case, Applicants are providing herewith a Declaration by Dr. Wolfert, a skilled artisan in this field. See paragraphs 1 and 2 of Dr. Wolfert's Declaration. Dr. Wolfert has reviewed teachings of both Packard et al. and Rao et al. See paragraph 3 of Dr. Wolfert's Declaration.

As a skilled artisan, Dr. Wolfert disagrees with the Examiner's suggestion that Packard et al. teaches the invention claimed in the instant patent application. See

paragraph 4 of Dr. Wolfert's Declaration. Specifically, Dr. Wolfert disagrees with the Examiner that Packard et al. teaches using the combined risks of CRP and Lp-PLA2 to assess the risk of cardiovascular disease in a patient. See paragraph 4 of Dr. Wolfert's Declaration. At the outset, Dr. Wolfert agrees with the review of Packard et al. set forth in the instant specification under the Clinical Review section at page 6. The instant specification states the results of Packard et al. show "[t]he association of Lp-PLA2 with CHD was independent of traditional risk factors such as LDL-cholesterol and other variables." As explained by Dr. Wolfert in paragraph 4 of his Declaration, the results in Table 5 of Packard are from multivariate analysis using different models (model 1, model 2 and variants of model 2) to determine how each marker (e.g. Lp-PLA2 or CRP) **individually** effects the risk of a coronary event. The statistical models Packard used show the **individual relative risk** for each marker. While the effects of other markers in the model of Packard et al. adjusted the individual risk of a single marker, as made clear in paragraph 4 of Dr. Wolfert's Declaration, such adjustment is not a combination of the risk of each marker as understood by those skilled in the art. Instead, as Dr. Wolfert explains in paragraph 4 of

his Declaration, the models taught by Packard et al. are used to refine or determine how predictive each marker may be **separately** in light of the predictive value of the other markers in the model. Packard et al. never combines the markers or determines the combined risk of markers. See paragraph 4 of Dr. Wolfert's Declaration. Contrary to the Examiner's suggestion, Table 5 of Packard et al. does not show to one skilled in the art a combination of Lp-PLA2 and CRP or a risk of CVD for such combination. See paragraph 4 of Dr. Wolfert's Declaration. Nor does the discussion on page 1152 of Packard et al. regarding CRP and Lp-PLA2 both being independent predictors of risk of coronary heart disease teach or suggest to the skilled artisan a combination of CRP and Lp-PLA2 risks to assess risk of coronary heart disease. See paragraph 4 of the Dr. Wolfert's Declaration.

MPEP 2111 and the case law are clear; claims are given their broadest reasonable construction in light of the specification as it would be interpreted by one of ordinary skill in the art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005). In addition to having reviewed Packard et al. and Rao et al., Dr. Wolfert is also very familiar with teachings of the instant specification.

See paragraph 2 of Dr. Wolfert's Declaration. Unlike Packard et al., the instant specification discloses combining markers Lp-PLA2 and CRP and then shows the effects of this specific combination on risk of cardiovascular disease in a patient. See paragraph 5 of Dr. Wolfert's Declaration. This is shown in Figure 7 of the specification which provides a graphical representation of data presented in Table 4.11 on page 32. See paragraph 5 of Dr. Wolfert's Declaration. As shown therein, patients with a high level of either CRP or Lp-PLA2 have somewhat elevated risk of CVD as compared to patients who have low levels of both markers, while patients having high levels of both CRP and Lp-PLA2 have a statistically significant elevated risk of CVD. See paragraph 5 of Dr. Wolfert's Declaration. The instant specification provides further examples wherein the combined risks of CRP and Lp-PLA2 are evaluated in patients with low LDL cholesterol levels and when the risks of CRP and Lp-PLA2 are combined from grouping patients by low, medium and high CRP and Lp-PLA2 levels. As explained by Dr. Wolfert in paragraph 5 of his Declaration, Figure 9 and data in the table at page 33 entitled Combined Risk of Lp-PLA2 and CRP Using Lp-PLA2 Tertiles and CRP Tertiles (1 and 3 ug/ml as cutpoints) for LDL<130 mg/dL (originally Table 4.11, renumbered herein as Table 4.13) show the risk for a patient

with low LDL cholesterol who has the highest levels of both Lp-PLA2 and CRP to be over three times higher than a patient with low cholesterol who has the highest level of either Lp-PLA2 or CRP (relative risks: 4.22/1.35=3.13 and 4.22/1.2=3.52). Thus, what is meant in the claims by combining the risks of Lp-PLA2 and CRP to assess the risk of cardiovascular disease in a patient is clear in light of teachings of the instant specification and is clearly distinguishable from teachings of Packard et al.

Besides teaching combining risks of Lp-PLA2 and CRP to assess the risk of CVD in a patient for the first time, another distinguishing characteristic between the instant invention and teachings of Packard et al. is that the instant invention teaches a method of determining patient risk of CVD by using risk ratios which take into account that a CVD event occurred in a patient and the time to such event. In paragraph 6 of Dr. Wolfert's Declaration he explains this difference as compared to teachings of Packard. Packard et al. teaches relative risks which only take into account that a CVD event occurred in a patient. See paragraph 6 of Dr. Wolfert's Declaration. By determining risk of CVD using risk ratios, Dr. Wolfert explains how the patent application for the first time teaches combining Lp-PLA2 and CRP risks to assess risk of a

CVD event and the time in the future that such a CVD event may occur. See paragraph 6 of Dr. Wolfert's Declaration. In particular, Figure 1 of the specification shows the proportion of patients in different combined CRP and Lp-PLA2 risk groups without a CVD event over time. Patients with high levels of both Lp-PLA2 and CRP had statistically significant decrease in time to a CVD event compared to patients with low levels of both Lp-PLA2 and CRP and compared to patients with a high level of either Lp-PLA2 or CRP. See paragraph 6 of Dr. Wolfert's Declaration. Thus, the patent application teaches the combination of Lp-PLA2 and CRP risks to assess the risk of CVD events in patients. Packard does not.

Further, "No doctrine of patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated." Deway & Almay Chem. Co. v. Mimex Co., 124 F.2d 986, 989, 52 USPQ 138, 142 (2d Cir. 1942). What was settled decades ago is still the law today. See Amgen, 314 F.3d at 1354, 65 USPQ2d at 1416. ("A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosure cited as prior art are not enabled."). The models taught by Packard et al. and

described by Dr. Wolfert in paragraph 4 of his Declaration as being used to refine or determine how predictive each marker may be **separately** in light of the predictive value of the other markers in the model are in no way enabling for the instant claimed invention which requires using the **combined risks** of Lp-PLA2 and CRPor LDL to assess the risk of CVD. Accordingly, Packard et al. cannot be considered an anticipating reference.

MPEP 2131 and the case law are also clear; a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Packard et al. in no way teaches or enables the skilled artisan the step of using the **combined risks** of Lp-PLA2 and CRP or LDL to assess the risk of CVD in the patient as claimed. This is made clear in Dr. Wolfert's Declaration. Accordingly, Packard et al., which does not teach or enable

all the elements of the claim, cannot anticipate the claim. See MPEP 2131.

Packard et al. alone and Packard et al. in view of Rao do not provide any suggestion to the skilled artisan the step of using the combined risks of Lp-PLA2 and CRP or LDL to assess the risk of CVD in the patient as claimed. The absence of any teaching in Packard to use the combined risks of Lp-PLA2 and CRP to assess the risk of CVD in a patient has been discussed in detail supra. Rao et al. clearly fails to remedy deficiencies in the teachings of Packard et al. as this reference is unrelated to determining the combined risk of Lp-PLA2 and CRP.

Further, as evidenced by paragraph 7 of Dr. Wolfert's Declaration, there were conflicting teachings with respect to Lp-PLA2 as a predictive marker of cardiovascular disease. Provided with Dr. Wolfert's Declaration is a reference by Blake et al. (J Am Coll Cardiol 2001 35(5):1302-6), which reported that Lp-PLA2 was not a significant predictor of future cardiovascular risk when adjusted for traditional cardiovascular risk factors. This reference is also discussed on page 7 of the instant patent application. Blake et al. published after Packard et al., but prior to filing of the instant patent application.

MPEP 2143.01 is clear; the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Blake et al. is clearly an analogous prior art reference which explicitly teaches away from both Lp-PLA2 and CRP being useful as predictors of cardiovascular risk and from combining Lp-PLA2 and CRP risks to assess risk of CVD. Accordingly, the prior art, when considered as a whole, does not provide any reasonable expectation of success with respect to the instant claimed invention.

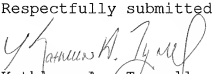
Accordingly, the cited combination of Packard et al. and Rao et al., which are silent with respect to the claimed step of using the combined risks of Lp-PLA2 and CRP or LDL to assess the risk of CVD in the patient, when viewed in light of Blake et al. which teaches away from Lp-PLA2 as a predictive marker of cardiovascular disease, can in no way render obvious the instant claimed invention

Withdrawal of these rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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